TECHNOLOGY OFFER

TITTLE: New non-L-subtypes Calcium channels blockers for applications on Nervous System Pathologies

BRIEF SUMMARY: Several years ago, *La Princesa Institute for Health Research* paid attention to the interesting properties of a natural product called gramine, in several in vitro models of neurodegeneration. Derivatives of this alkaloid were described to possess voltage-gated calcium channel blocking activity. Hence, we proposed the synthesis of new derivatives in order to improve neuroprotective properties, enhancing pharmacokinetic parameters and featuring a good blood-brain barrier penetration.

PRODUCT: The family of chemical compounds are derivatives of the (1H)-indole-3-ylmethyl)dimethylamine. Twenty compounds were evaluated, possesing neuroprotective properties in in vitro models of neurodegeneration. They also blocked calcium channels, being the best blocker the 1-benzyl-5-methyl-3-(piperidin-1-ylmethyl)-1H-indole, named as ITH12657

MAIN FEATURES: There are very few calcium channels blockers targeting those named non-L. Moreover, the few ligands that block T-, N- or P/Q-type calcium channels are not selective, as most of them also block L-type channels. In addition, many of them are peptides or peptidomimetics, so they have a very poor blood-brain penetration, what limits their use in central diseases.

MECHANISM OF ACTION: The new compounds, highlighting that called ITH12657, blocked voltage-gated calcium channel, with selectivity to those classified as non-L, that are mainly P/Q and N-type calcium channels. They reduced calcium entry stimulated by depolarization by about 30% in neuroblastoma cells, and 4 of them blocked calcium currents in bovine chromaffin cells efficiently. The compound ITH12657 blocked calcium current by 40%, a blockade that was added to that elicited by nifedipine when this L-type calcium channel blocker was exposed to cells. Such blocked was masked in presence of toxines selective to non-L channels.

THERAPEUTIC AREA: **Neuropathic pain**. Otherwise, due to the key role of voltage-dependent Ca2+ channels and their control of the cell Ca2+ levels in neurons, these compounds can regulate the Ca2+ overload described in several pathologies of the nervous system, such as neurodegenerative (Alzheimer's, Parkingson's, Amyotrophyc Lateral Esclerosis), stroke, other types of pain, and epilepsia, and be used as medicines to treat these diseases

CURRENT STATUS:

- Chemical Synthesis: Subgram scale and salinization to improve water solubility
- Cell culture-based In vitro assays: (a) Compounds blocked Ca2+ increase induced by depolarization in SH-SY5Y cells, (b) protected efficiently SH-SY5Y cells against a model of Tau hyperphosphorylation-dependent diseases, and (c) protected efficiently rat motor cortex neurons against a model of Ca2+ overload
- Tissue preparations-based In vitro assays: Selected compounds protected rat hippocampal slices against a model of Ca2+ overload and excitotoxicity
- Patch-Clamp experiments: Selected compounds blocked Ca2+ entry via voltage-dependent Ca2+ channels in chromaffin cells. The best one did not affect the cardiovascular-related L-type, but the P/Q and N-type Ca2+ channels, targets for the treatment of neurophatic pain.

PATENT STATUS: **P201500354**. PRIORITY DATE: 05/14/2015

COOPERATION WITH INDUSTRY: We search for companies with interest to license our research work, capable to further investigate its therapeutic applicability. In addition, we seek to extend this research to optimized compounds, evaluating their pharmacological activities in the models we skilled. Thus, we are open to make a collaboration with companies interested in granting our project to keep developing new calcium channel blockers

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